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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,026	07/30/2001	Rosanne M. Crooke	ISPH-0588	1035

26259 7590 11/19/2002

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EXAMINER
GIBBS, TERRA C

ART UNIT	PAPER NUMBER
1635	10

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/918,026	Applicant(s) CROOKE ET AL.	
	Examiner Terra C. Gibbs	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-20* is/are pending in the application.

4a) Of the above claim(s) *15-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2 and 4-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office Action is a response to the Restriction Requirement filed September 26, 2002, in Paper No. 8.

Claims 1, 2 and 4-14 are pending in the instant application.

Claims 15-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

Claims 1, 2 and 4-14 have been examined as indicated below.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-14) in Paper No. 9 is acknowledged. The traversal is on the ground(s) that all of the claims are related to the single concept of modulating the expression of acyl CoA cholesterol acyltransferase-2. Further, Applicant argues that a search of literature relating to acyl CoA cholesterol acyltransferase-2 would clearly reveal art relating to all of the claims, and therefore would not place an undue burden on the examiner. This is not found persuasive because, as argued in the restriction requirement (Paper No. 8), where claims are drawn to a product, process of making and process of using, restriction may be required where the process of making and product made are distinct according to the guidelines set forth in MPEP 806.05(f) (see MPEP 806.05(i)), as was demonstrated for the product and process of using of the instant application.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2 and 4-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cases et al. [WO 99/67368] and Sturley [WO 97/45439] in further view of Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288).

Claims 1, 2 and 4-14 are drawn to a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 (SEQ ID NO. 3); wherein said compound specifically hybridizes with the nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 and inhibits the expression of acyl CoA cholesterol acyltransferase-2; wherein the compound is an antisense; wherein the antisense oligonucleotides comprises at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide; and a compound 8 to 50 nucleobases in length which specifically hybridizes with at least an 8-nucleobase portion of an active site on a nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 (SEQ ID NO: 3); and a composition comprising the compound

8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system.

Sturley teach a nucleic acid having a sequence complementary to an isolated nucleic acid which encodes an acyl CoA cholesterol acyltransferase-2 and prevents translation of the mRNA (see claims 1, 33 and 42).

Cases et al. teach a method for inhibiting the activity of acyl CoA cholesterol acyltransferase-2 (ACAT-2) via an agent that inhibits the activity of ACAT-2 (see Claim 9 and SEQ ID NOs. 2 and 4). Cases et al. further teach the agent may be an antisense compound which down-regulation expression of ACAT-2 in cells, for example (see page 24, last paragraph and page 28, lines 15-27). Cases et al. finally teach the antisense compound will be generally about 20 nucleotides in length (see page 28, last paragraph) and may have chemical modifications, including a phosphorothioate linkage or 2'-O-methyl sugars (see page 29, last two paragraphs).

Sturley and Cases et al. do not teach wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide; and a composition comprising the compound 8 to 80 nucleobases in length targeted to a nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system.

Baracchini et al. teach modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases. Baracchini et al.

further teach antisense oligonucleotides with phosphorothioate modified backbones (see column 6, line 37)... with at least one modified sugar moiety and a modified 2'-O-methoxyethyl sugar moieties (see Table I)... with modified nucleobases, such as 5-methylcytosine (see column 7, lines 15-25). Baracchini et al. finally teach an antisense oligonucleotide as a chimeric oligonucleotide (see column 8, lines 12-19)

Fritz et al. teach a composition comprising an antisense oligonucleotide and a pharmaceutically acceptable carrier or diluent comprising a colloidal dispersion system. Fritz et al. further teach that oligonucleotides, in combination with steric stabilizers, exhibit high colloidal stability with low toxic side effects as required for biological experiments in cell culture and *in vivo* (see page 287, last paragraph).

It would have been obvious to make antisense oligonucleotides encoding acyl CoA cholesterol acyltransferase-2 since the prior art has asserted that acyl CoA cholesterol acyltransferase is an enzyme involved in cholesterol esterification and cholesterol absorption (Cases et al.). One of ordinary skill in the art would have had a reasonable expectation of success in making antisense oligonucleotides targeting acyl CoA cholesterol acyltransferase-2 since Cases et al. taught an agent consisting of a nucleic acid sequence consisting of all or a part of acyl CoA cholesterol acyltransferase-2 will decrease or down regulate the expression of acyl CoA cholesterol acyltransferase-2 and Sturley taught a nucleic acid having a sequence complementary to an isolated nucleic acid which encodes an acyl CoA cholesterol acyltransferase-2 and prevents translation of the mRNA. One of ordinary skill in the art would have been motivated to modify antisense oligonucleotides since the prior art has taught the desirability of such oligonucleotides are often preferred over native forms because of enhanced

cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases and the exhibition of high colloidal stability with low toxic side effects as required for biological experiments (Baracchini et al. and Fritz et al.).

It would have been obvious at the time the invention was made to combine the teachings of Sturley and Cases et al. with the methods of Baracchini et al. and Fritz et al. Furthermore, one of ordinary skill in the art would have reasonably expected to be successful since Cases et al. taught an agent consisting of a nucleic acid sequence consisting of all or a part of acyl CoA cholesterol acyltransferase-2 will decrease or down regulate the expression of acyl CoA cholesterol acyltransferase-2 and Sturley taught a nucleic acid having a sequence complementary to an isolated nucleic acid which encodes an acyl CoA cholesterol acyltransferase-2 and prevents translation of the mRNA and since Baracchini et al. and Fritz et al. taught the successful use of modified antisense oligonucleotides enhance affinity for nucleic acid target and exhibit high colloidal stability with low side effects. The invention as a whole would therefore have been obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
November 11, 2002

SEAN McGARRY
PRIMARY EXAMINER